

# Evaluation of Immune Serum Globulin for Control of Infectious Hepatitis

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STOKES (1) working with a summer camp population, Gellis (2) with U.S. Armed Forces personnel, and Havens (3) with children in an orphanage reported independently in 1945 that immune serum globulin effectively prevented infectious hepatitis. Subsequently, other studies (4-10) of populations in institutions and among families involved in outbreaks confirmed and extended these observations.

In contrast to these studies of restricted populations, Clark (11) in 1960 reported on a general population. His was the first study on the use and effectiveness of immune globulin for prophylaxis of infectious hepatitis in an open population. Though our study was somewhat different in design, its purpose was similar. It was undertaken to evaluate a local program in which private physicians and the Seattle-King County (Wash.) Department of Public Health collaborated.

## Methods

Infectious hepatitis cases reported to the Seattle-King County Department of Public Health during January, March, and May of 1963 were index cases for this study. Between July 23 and August 30, 1963, one of the authors

(Noble) attempted to interview a knowledgeable adult, usually the mother, in each of the 128 households in which an index case had been reported. (Two of the 129 index cases had occurred almost simultaneously in the same household.)

The interviewer sought information on all persons residing in these households whether or not they were related to the persons with index cases. He noted the name, age, sex, symptoms, and dates of any illness occurring within 60 days of onset of the index case for each person on the household roster. He asked respondents who were uncertain about dates or other facts to consult a calendar or other household members for assistance. Reliability was gauged by matching the respondents' answers with facts already known to the interviewer from the original case report forms or from physicians' records, such as dates of onset of the index cases and dates on which immune globulin was administered. In most instances, the answers agreed with the record. In those that did not agree, the answers were within a few days of that recorded.

Interviews by telephone or by home visit were ultimately successful in 121 of the households with reported cases, or for 95 percent of the cases:

<i>Interviews attempted</i>	<i>Number of households</i>
Successful .....	121
Telephone .....	94
Visit .....	27
Unsuccessful .....	7
Telephone (refused to cooperate) .....	1
Visit (moved, no response to certified letter) .....	2
Visit (moved, whereabouts unknown) ..	4

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In one household, Noble made 17 attempts before completing a satisfactory interview. In all, 277 telephone calls and 44 visits entailing 576 miles of travel were required.

Elimination of the 7 households that we were unable to interview and of 6 in which the diagnosis of the reported case was subsequently revised by the attending physician left 115 households for study. In these, 513 persons presumably had been exposed to infectious hepatitis.

Physicians in private practice had reported 103 of the 116 index cases; health department casefinding had discovered the remainder. Of the 58 cases which occurred among household contacts of the index cases, 39 (67 percent) had been officially reported to the health department. Only persons with generalized jaundice, scleral icterus, or dark urine with light-colored stools were classified for purposes of this study as having secondary cases of infectious hepatitis.

Intervals from onset of the index case to our

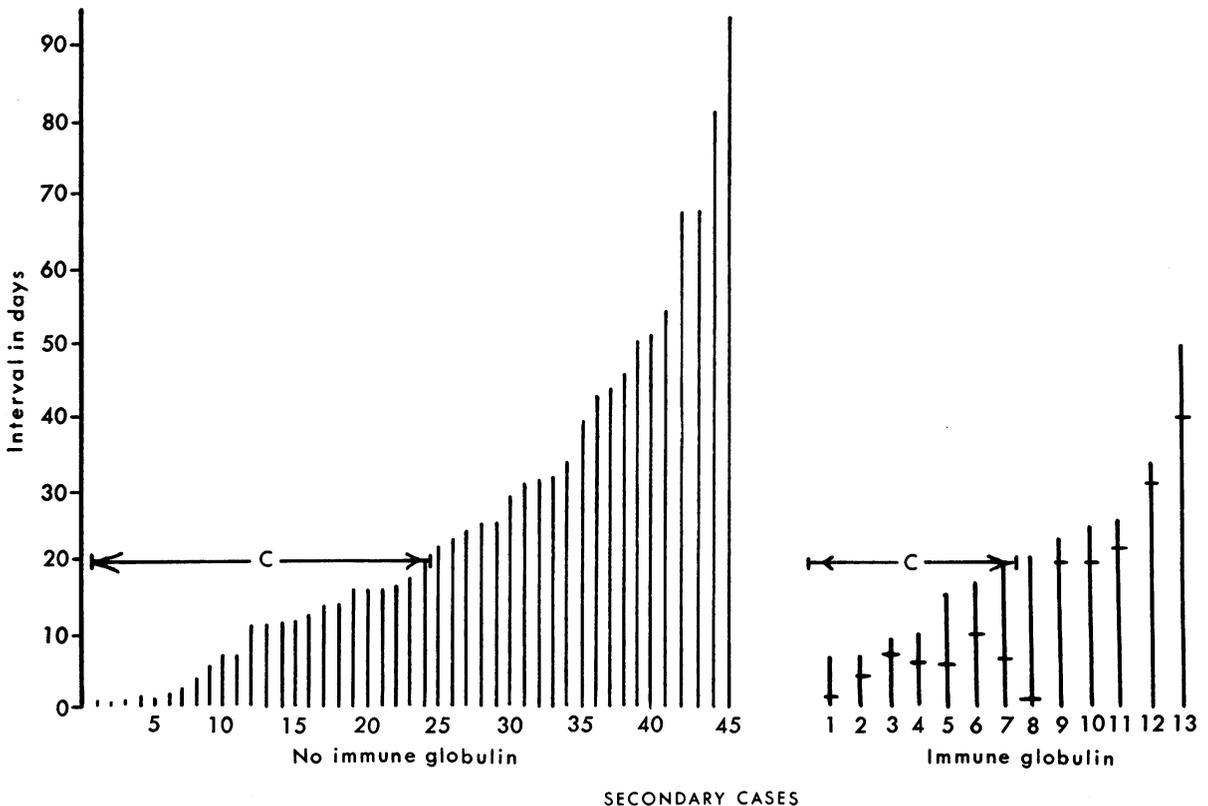
interview ranged from 7 to 34 weeks. How this might have affected respondents' recollection of illness occurrences can be deduced from the following list of numbers of index cases and associated secondary cases by month of onset.

Month	Index cases	Secondary cases
January -----	40	20
March -----	36	16
May -----	40	20
Total -----	116	96

The total of 116 index cases includes 2 cases occurring in the same household. The ratio of index cases to secondary cases is the same for each of the 3 months. Bias, if present from delayed interviewing, was distributed remarkably equally.

The health department and most private physicians routinely gave a dose of 0.02 milliliter per pound of body weight; some physicians

**Interval from onset of index case to onset of secondary cases in same household for those receiving and those not receiving immune globulin, Seattle-King County, Wash.**



NOTE: Tops of vertical bars indicate onset; "C" indicates cases assumed to be coprimary on basis of Clark's criteria (11); transverse marks indicate elapsed time from onset of index case to immune globulin administration.

**Characteristics of 503 household contacts of 116 cases of infectious hepatitis, showing risk of infection for recipients and nonrecipients of immune globulin prophylaxis, Seattle-King County, Wash.**

Characteristic	Immune globulin			No immune globulin		
	Contacts	Cases	Percent	Contacts	Cases	Percent
Age of household contacts:						
0-4 years.....	49	3	6	58	8	14
5-19 years.....	131	6	5	50	17	34
20 years and over.....	150	4	3	65	20	31
Age of persons with index cases:						
0-4 years.....	18	1	6	26	19	35
5-19 years.....	144	7	5	75	17	23
20 years and over.....	168	5	3	72	19	26
Sex of household contacts:						
Male.....	162	8	5	92	18	20
Female.....	168	5	3	81	27	36
Number of persons in household:						
2.....	16	1	6	17	4	24
3.....	40	1	2	23	9	39
4.....	93	7	8	31	8	26
5.....	44	2	5	26	8	31
6.....	47	0	-----	19	1	5
7.....	19	0	-----	16	3	19
8.....	14	1	7	18	7	39
9 or more.....	57	1	2	23	5	22

approximated the total dose to the nearest 2 milliliters.

**Results**

Of 513 household contacts of 116 persons with infectious hepatitis, 340 (67 percent) received immune globulin prophylaxis. Of these, 181 (53 percent) received commercially produced immune globulin allocated to the health department by the American National Red Cross, and 156 (46 percent) were given immune globulin acquired through pharmaceutical outlets by privately practicing physicians. Ten persons were given immune globulin after the onset of what later proved to be icteric illness; five of these were treated by the health department and five by a personal physician. These cases are not included in results of this study. In addition, one person obtained immune globulin from a health department in an adjacent county, a second from a military medical facility, and a third from his mother who was a nurse.

In the figure, cases among household contacts which occurred subsequent to an index case are ranked on the horizontal axis by the interval in days from onset of index case to onset of subsequent case (vertical axis). The point within this interval at which immune globulin was

given is shown for the 13 cases occurring in the treated group. The crude attack rate was 3.9 percent ( $\frac{13}{330} \times 100$ ) compared to 26.0 percent ( $\frac{45}{173} \times 100$ ) for the untreated group.

Clark (11) assumed that all those in his study becoming ill with icterus within 20 days after onset of the index case probably were exposed at the same time as the index case (co-primary). The lines labeled "C" on the figure delineate such cases in this study. There were 7 such cases in the treated group and 24 in the untreated. Subtracting these cases from both numerator and denominator used in calculating the crude attack rates gives rates of 1.9 percent ( $\frac{6}{323} \times 100$ ) for the treated and 14.1 percent ( $\frac{21}{149} \times 100$ ) for the untreated.

Applying the rate of 14.1 percent (untreated group) to the 323 persons (treated group) gives a hypothetical number of cases which might be expected without treatment. Thus,  $14.1\% \times 323 = 45.6$ , or 46 cases. Six cases actually occurred in this population. The difference indicates the number prevented. Effectiveness is calculated to be 87 percent ( $\frac{40}{46} \times 100$ ).

The interval from immune globulin administration to onset in the 7 cases coming under Clark's criterion can be seen in the figure

to range from 2 to 13 days (mean 6.3 days, median 6 days). In these cases it seems likely that immune globulin was given too long after exposure to be effective. Cases numbered 9—13 can also be interpreted as delayed prophylaxis. The only frank failure seems to be case number 8 in which immune globulin was given 1 day following presumed exposure to infectious hepatitis and icteric illness became apparent 20 days later. Interestingly, cases numbered 1—6 received immune globulin from the health department and those numbered 7—13 from privately practicing physicians.

The marked difference in rate of subsequent icteric illness occurrence between the two groups (immune globulin, no immune globulin) may have resulted from other factors associated with exposure and susceptibility. The data tabulated in the table bear indirectly on this possibility. In every category there is a marked difference in risk in favor of those who received immune globulin.

The data in the table also show that the proportion of small children (0-4 years) in the no-immune-globulin group was more than twice that in those who received immune globulin ( $\frac{58}{173}=0.33$  compared with  $\frac{49}{330}=0.15$ ). Similarly, the index case occurred in a small child three times as often in the untreated group as in the treated one ( $\frac{26}{173}=0.15$  compared with  $\frac{18}{330}=0.05$ ). The sexes were distributed nearly equally in the two groups. Proportionately more persons lived in households of seven persons or more in the group which did not receive immune globulin.

## Discussion

Originally 122 index cases from 121 households were available for study, but 6 cases (5 percent) were not used because the attending physician, upon further observation of the patient, revised his original diagnosis. The remainder were probably bonafide infectious hepatitis cases from the clinical point of view. The predominant mode of spread of the disease was personal contact with someone who had either an apparent or inapparent case of infectious hepatitis; small outbreaks from a common source occurred both before and after the study period, but none were identified during it.

Two-thirds of all the household contacts received immune globulin prophylaxis, about one-half obtaining it from their physicians and the other half from the health department. By contrast, only about one-half of the contacts in the study by Clark (11) were treated. In both studies, the secondary attack rate, based on similar diagnostic criteria, was much lower among recipients of immune globulin than among non-recipients, with resulting calculated effectiveness of a high order. Our study showed that timing of immune globulin administration was frequently inappropriate to the presumed exposure. The health department and practicing physicians contributed about equally to this fault. This imperfect timing may be looked upon as a program failure, although timing of treatment is often beyond control of the treating facility. Those not receiving immune globulin prophylaxis may also be considered program failures since considerable illness could probably have been prevented if they had been treated. One may postulate from the data in the table that large families with small children find it difficult to avail themselves of immune globulin prophylaxis even when it is free of charge. Perhaps transportation to a treating facility is difficult. But this does not account for all those who did not receive immune globulin. Ignorance, indifference, forgetfulness, or inadvertent delay may also have contributed to this result.

Despite difficulties inherent in a study of this sort it seems reasonable to conclude, as did Clark, that such a program was highly effective in reducing the occurrence of overt icteric illness.

McCollum (12) has pointed out epidemiologic similarities between poliomyelitis and infectious hepatitis, noting that in both, with improving environmental sanitation, many persons escape mild immunizing childhood infection and remain susceptible into adulthood. Indeed, in this study, attack rates for those 20 years and older were of about the same magnitude as those 5-19 years (see table). Stokes (13) and later Krugman (14) showed that immune globulin had a modifying rather than a truly prophylactic effect in infectious hepatitis. For example, if immune globulin is given before exposure, incidence of infection is about the same as among uninoculated persons.

Among those inoculated, sophisticated diagnostic measures must be employed to avoid overlooking a mild or inapparent infection. The net effect of inoculation of such persons is suppression of overt icteric illness and inducement of passive-active immunization. An adult, spared a confining illness by immune globulin and pursuing his usual activities, may transmit infection to others just as a person with a naturally occurring nonicteric case does. On a community scale, immune globulin may thus possibly augment rather than prevent the occurrence of infectious hepatitis. This speculation is not intended to deter physicians from using immune globulin for infectious hepatitis prophylaxis but simply to acquaint them with a possible unforeseen consequence of its use. Definitive study of this hypothesis must await development of specific laboratory tests.

### Summary

To evaluate the pattern of use and the effectiveness of immune globulin prophylaxis in an open population, 513 household contacts of 116 patients with infectious hepatitis were studied. The cases were reported to the Seattle-King County (Wash.) Department of Public Health during January, March, and May 1963. Two-thirds of the contacts were treated prophylactically, about one-half by the health department and the other half by privately practicing physicians. The untreated group had proportionately more young children (0-4 years of age) and larger households than the treated group. This may have contributed to their failing to receive treatment in this collaborative program.

Effectiveness of immune globulin prophylaxis was calculated to be 87 percent in this study. In all but one case, analysis of the failures revealed less than optimal timing of administration in relation to presumed exposure. With doses of approximately 0.02 milliliter per pound of body weight given within 1 week of actual exposure the expectation of icterus suppression should approach 100 percent.

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